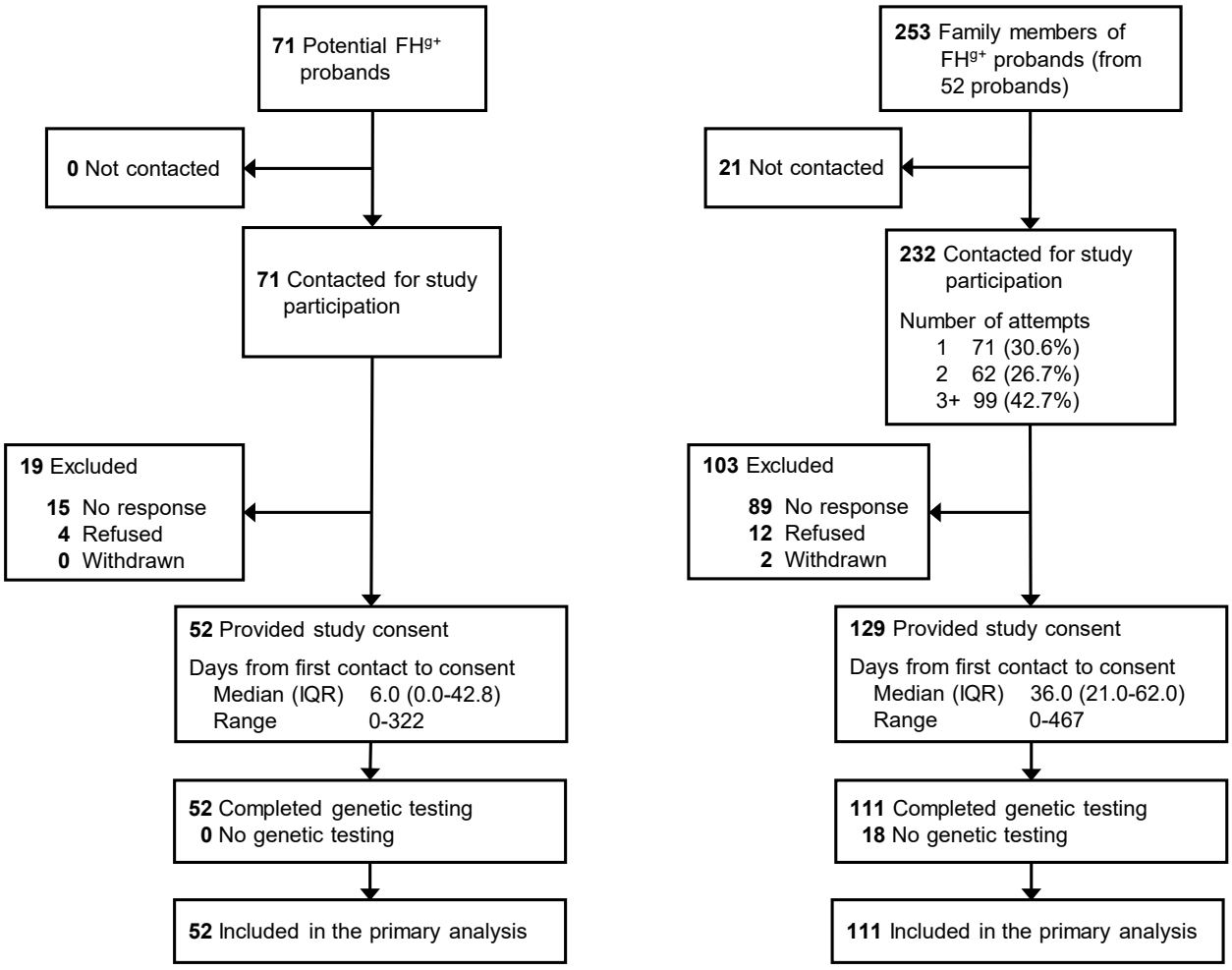
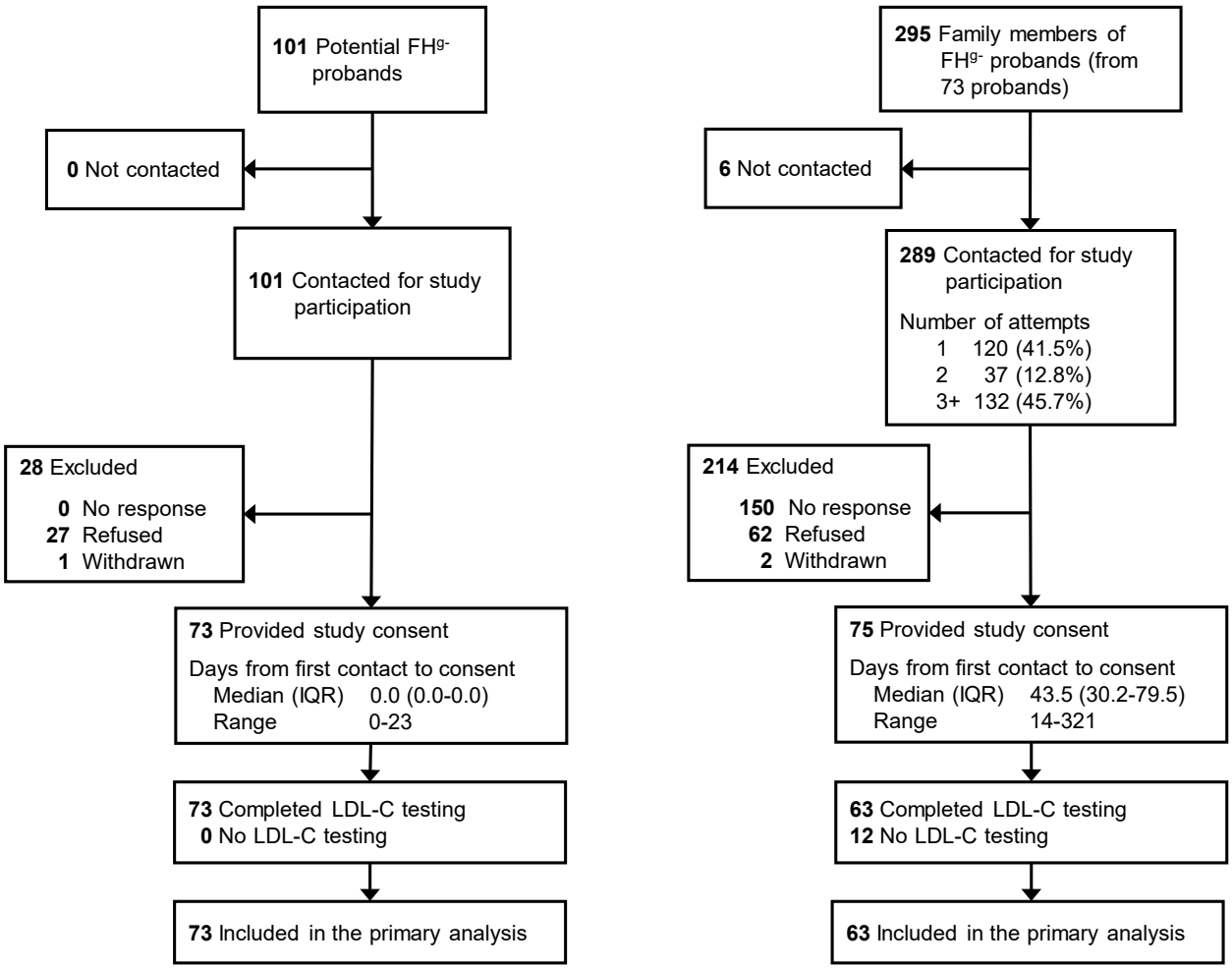
SUPPLEMENTAL MATERIAL

Supplemental Figure 1. Enrollment Numbers in FH^{g+} Study Arm



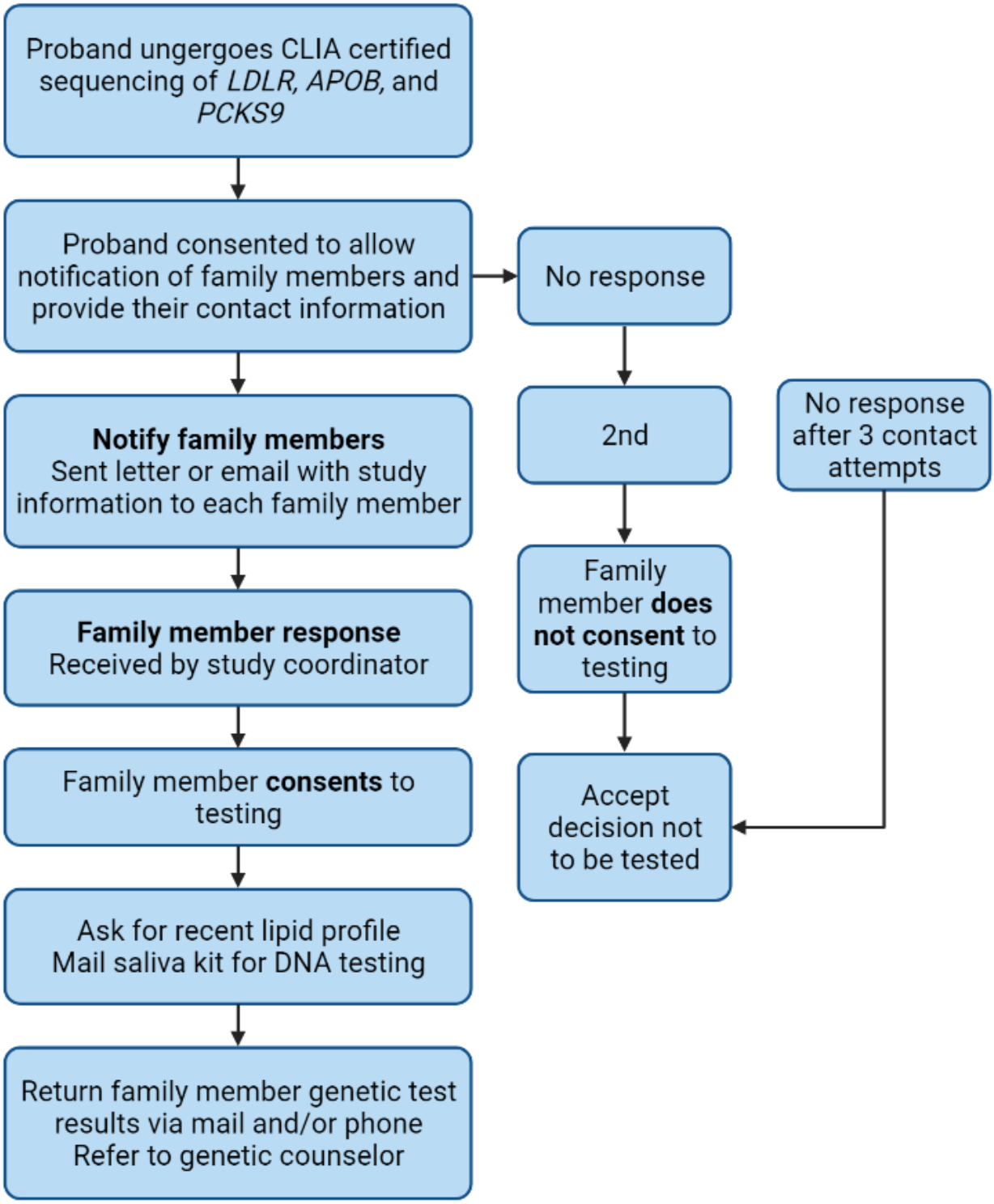
Abbreviation: FH^{g+}, familial hypercholesterolemia with a pathogenic variant.

Supplemental Figure 2. Enrollment Numbers in FH^{g-} Study Arm



Abbreviations: FH^{g-}, familial hypercholesterolemia without a pathogenic variant; LDL-C, low-density lipoprotein cholesterol.

Supplemental Figure 3. Participant Recruitment Flow Diagram



Cascade Testing Beyond First-Degree Relatives

FH^{g+} and FH^{g-} probands were asked to provide the study team a list of relatives at the time of consent.

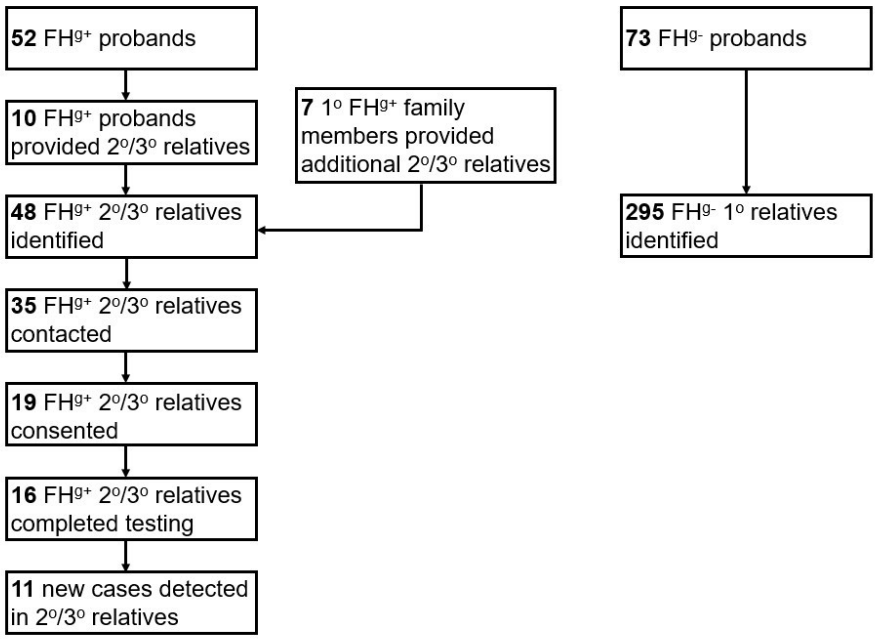
Of 52 FH^{g+} probands, 10 provided family member contact information for 48 second- and third-degree relatives (**eFig 4**).

Additionally, when a new case in an FH^{g+} family member (defined as presence of a P/LP variant) was detected, they were mailed a copy of their results along with 2 copies of the consent form that provided the study team permission to contact relatives. Of the 37 new cases detected in first-degree relatives, 7 consented for the study team to contact the family members they listed (**eFig 4**). The relatives they provided were listed in the context of their relation to the original proband.

The study team required variant confirmation in a first-degree relative prior to contacting second-degree relatives and so on. In all, 35 second and third-degree relatives were contacted by the study team with 19 consenting to the study, 16 completing genetic testing, and 11 new cases (defined as presence as a P/LP variant) were detected.

Of 73 FH^{g-} probands, none provided contact information for second- or third-degree relatives.

Supplemental Figure 4. Cascade Testing Beyond First-Degree Relatives



Supplemental Table 1. FH^{g+} Proband Variant List

Gene	P/LP Variant (n=52)
LDLR	c.1187-2A>G (n=1)
LDLR	c.1238C>T (n=1)
LDLR	c.1246C>T (n=1)
LDLR	c.131G>A (n=1)
LDLR	c.1329G>C (n=2)
LDLR	c.1358+2T>A, splice donor (n=1)
LDLR	c.1359-1G>A (n=1)
LDLR	c.1444G>A (n=2)
LDLR	c.1474G>A (n=1)
LDLR	c.1576C>T (n=1)
LDLR	c.1586+5G>A, intronic (n=1)
LDLR	c.1640T>C (n=1)
LDLR	c.1860G>A (n=1)
LDLR	c.2054C>T (n=1)
LDLR	c.254_265delTCTGGAGGT (n=1)
LDLR	c.259T>G (n=4)
LDLR	c.313+1G>A, splice donor (n=2)
LDLR	c.324_325delisnTC (n=1)
LDLR	c.501C>A (n=1)
LDLR	c.502G>C (n=1)
LDLR	c.551G>A (n=1)
LDLR	c.644G>A (n=1)
LDLR	c.662A>G (n=1)
LDLR	c.782G>T (n=1)
LDLR	c.796G>A (n=2)
LDLR	c.798T>A (n=2)
LDLR	c.862G>A (n=1)
LDLR	Del Exons 2-3 (n=1)
LDLR	Del Exons 16-18 (n=1)
LDLR	Del Exon 18 (n=1)
PCSK9	c.94G>A (n=1)
APOB	c.10580G>A (n=13)

Supplemental Table 2. Lipid Lowering Treatment for Probands Who Provided Consent and Completed Testing

Characteristic	Proband Type		*P* value[a]
	FH^{g+} (n = 52)	FH^{g-} (n = 73)	
Ever used a statin	50 (96.2%)	68 (93.2%)	.472
At time of highest LDL-C measurement			
Lipid lowering treatment	14	4	<.001
Only statin use	12	4	.004
Type of statin[b]			--
Atorvastatin	6	1	
Lovastatin	2	1	
Rosuvastatin	1	1	
Simvastatin	3	1	
Only non-statin use	1	0	.234
Type of non-statin[b]			--
Evolocumab	1	0	
Combined statin and non-statin use	1	0	.234
Type of medications[b]			--
Rosuvastatin and ezetimibe	1	0	
Current use at follow-up			
Lipid lowering treatment	47 (90.4%)	62 (84.9%)	.368
Only statin use	27	59	<.001
Type of statin[b]			--
Atorvastatin	15	36	
Pravastatin	0	3	
Rosuvastatin	9	8	
Rosuvastatin and simvastatin	1	0	
Simvastatin	2	12	
Only non-statin use	2	3	.941
Type of non-statin[b]			--
Ezetimibe	2	3	
Combined statin and non-statin use	18 (34.6%)	0 (0.0%)	<.001
Type of medications[b]			--
Atorvastatin and evolocumab	1	0	
Atorvastatin and ezetimibe	6	0	
Atorvastatin, evolocumab, and ezetimibe	2	0	
Rosuvastatin and evolocumab	1	0	
Rosuvastatin and ezetimibe	6	0	
Rosuvastatin, evolocumab, and ezetimibe	2	0	

Values are n (%).[a] Chi-square test, or reported as -- if not tested; [b] Percentages were calculated among people with the corresponding type of treatment.

Abbreviations: FH^{g+}, familial hypercholesterolemia with a pathogenic variant; FH^{g-}, familial hypercholesterolemia without a pathogenic variant; LDL-C, low-density lipoprotein cholesterol.

Supplemental Table 3. Geographic Location of Family Members Who Provided Consent and Completed Testing

Characteristic	Proband Type	
	FH^{g+} (n = 111)	FH^{g-} (n = 63)
Region[a]		
West north central	**72 (64.9%)**	**50 (79.4%)**
Other	**39 (35.1%)**	**13 (20.6%)**
Mid-Atlantic	4 (3.6%)	2 (3.2%)
East north central	10 (9.0%)	4 (6.3%)
New England	2 (1.8%)	2 (3.2%)
South Atlantic	6 (5.4%)	1 (1.6%)
East south central	1 (0.9%)	0 (0.0%)
West south central	4 (3.6%)	0 (0.0%)
Mountain	6 (5.4%)	3 (4.8%)
Pacific	6 (5.4%)	1 (1.6%)
State		
Minnesota	**60 (54.1%)**	**47 (74.6%)**
Other	**51 (45.9%)**	**16 (25.4%)**
Arizona	3 (2.7%)	2 (3.2%)
California	5 (4.5%)	1 (1.6%)
Colorado	2 (1.8%)	0 (0.0%)
Connecticut	1 (0.9%)	1 (1.6%)
Florida	5 (4.5%)	0 (0.0%)
Georgia	1 (0.9%)	0 (0.0%)
Iowa	5 (4.5%)	2 (3.2%)
Illinois	0 (0.0%)	1 (1.6%)
Indiana	2 (1.8%)	0 (0.0%)
Maryland	0 (0.0%)	1 (1.6%)
Michigan	2 (1.8%)	1 (1.6%)
Missouri	2 (1.8%)	0 (0.0%)
Mississippi	1 (0.9%)	0 (0.0%)
Montana	0 (0.0%)	1 (1.6%)
North Dakota	5 (4.5%)	0 (0.0%)
Nebraska	0 (0.0%)	1 (1.6%)
New Hampshire	1 (0.9%)	1 (1.6%)
New York	3 (2.7%)	1 (1.6%)
Oklahoma	1 (0.9%)	0 (0.0%)
Pennsylvania	1 (0.9%)	1 (1.6%)
Texas	3 (2.7%)	0 (0.0%)
Utah	1 (0.9%)	0 (0.0%)
Washington	1 (0.9%)	0 (0.0%)
Wisconsin	6 (5.4%)	2 (3.2%)

Values are n (%).[a] Regions of the United States as defined by the U.S. Census Bureau.

Abbreviations: FH^{g+}, familial hypercholesterolemia with a pathogenic variant; FH^{g-}, familial hypercholesterolemia without a pathogenic variant.

Supplemental Table 4. Participation Rate, Uptake, and Yield of New Cases[a] by Proband Type Among First-Degree Family Members

Parameter with 95% CIs[b]	Proband Type		*P* value
	FH^{g+}	FH^{g-}	
Number of probands	52	73	--
Number of family members			
All identified	202	295	--
With consent	110	75	--
With consent and completed testing	95	63	--
Who met criteria as a new case	37	17	
Mean number of family members per proband			
All identified	3.9 (3.3-4.5)	4.0 (3.4-4.7)	.692
With consent	2.1 (1.6-2.6)	1.0 (0.7-1.3)	<.001
With consent and completed testing	1.8 (1.4-2.3)	0.9 (0.6-1.1)	<.001
Who met criteria as a new case	0.7 (0.5-1.0)	0.2 (0.1-0.3)	<.001
NCIC[c]	0.712 (0.481-0.962)	0.233 (0.123-0.343)	<.001
Uptake of cascade testing[d]	47.0% (36.8-55.9)	21.4% (15.8-26.7)	<.001
Yield of cascade testing[e]	38.9% (30.8-48.1)	27.0% (16.7-38.5)	.092

Abbreviations: CIs, confidence intervals; DLCN, Dutch Lipid Network Clinic; FH^{g+}, familial hypercholesterolemia with a pathogenic variant; FH^{g-}, familial hypercholesterolemia without a pathogenic variant; LDL-C, low-density lipoprotein cholesterol; NCIC, new case per index case.

[a] New cases are defined as family members with consent who completed testing who had pathogenic variants among relatives of FH^{g+} probands, and who had LDL-C ≥155 mg/dL among relatives of FH^{g-} probands.

[b] Confidence intervals were calculated using bootstrapping over 1,000 iterations. Each bootstrap sample selected 52 FH^{g+} or 73 FH^{g-} probands (simple random sampling with replacement) and their corresponding family members. Each parameter was calculated separately within each bootstrap sample and the 2.5th and 97.5th percentiles across all bootstrap samples defined the 95% confidence intervals.

[c] NCIC was calculated as the number of family members who met criteria as a new case divided by the total number of probands.

[d] Uptake was defined as the proportion of family members who consented and completed testing among all identified family members.

[e] Yield was defined as the proportion of family members who met criteria as a new case among family members who consented and completed testing.